Measles

This is an exciting time in the history of measles. Substantial progress toward the elimination of measles in the Americas has been achieved already, but there are threats to our success. **Your** vigilance on surveillance and vaccination will make a difference in humanity's struggle against this virus. The measles chapter in the book begins on page 115. Take a minute now to turn there if you want to follow along.

Measles is a highly contagious viral illness that has been around for a long time. It was thought to be the same disease as smallpox until the tenth century and it took another 700 years before the clinical characteristics of measles were clearly described. In 1846 it was demonstrated that there was lifetime immunity following the disease.

In 1954 the virus was isolated by John Enders, only 5 years after he isolated poliovirus. Dr. Ender's work led to the production of a measles vaccine in 1963. Measles is also known as rubeola. We prefer to use the term measles, rather than rubeola, to avoid confusion with rubella.

Measles virus is a paramyxovirus with an RNA genome. It is the cousin of the viruses that cause canine distemper and a disease of cattle called rinderpest. It is possible that in the remote past, the ancestor of measles was an animal virus that made a species jump from dogs or cows to humans. Measles virus is rapidly inactivated by heat and light, but can survive up to 2 hours in the air of a poorly ventilated room. Hemagglutinin is a protein in the outer coat of measles virus. It is an important surface antigen for 2 main reasons. First, antibodies to hemagglutinin produce immunity to measles virus. Second, subtle changes in the gene coding for hemagglutinin act like a fingerprint. As you would guess, this genetic fingerprinting is highly technical, but it allows scientists to trace the relationship back and determine the country of origin for a particular measles virus.

It is difficult to eradicate a disease that's easily confused with others. Fortunately, the clinical features of measles are fairly distinct, at least **after** the rash appears. Unfortunately, most of the transmission takes place **before** the rash appears.

After an incubation period of 10 to 12 days, there is a stepwise increase in temperature to 103^{o} Fahrenheit, or higher. What usually follows is the classic triad of cough, coryza or runny nose, and conjunctivitis or pink eye. An astute observer may see Koplik spots – a rash found on mucous membranes a day or two before the cutaneous rash. This prodrome usually lasts 2 to 4 days. The rash appears about 14 days after exposure and is caused by deposits of measles antibody. The rash is maculopapular, and appears first on the face. During the next 2 or 3 days it descends to the trunk and then to the arms and legs. The rash fades in the order of appearance. Many of you saw measles when it was common in the late 1950s and early 1960s, or during the outbreaks in the late 1980s and early 1990s. For those of you who have not seen it, here is a visual aid.

This is a child with measles prodrome. Measles prodrome usually produces a moderate illness. Notice the coryza, or runny nose, and her red teary eyes, indicative of conjunctivitis. This is measles at about 2 days into the rash, or 5 to 6 days into the illness. The rash is maculopapular. The rash also demonstrates coalescence, when the discrete macules coalesce into a larger red skin lesion. Cough is almost universal with measles. The rash is typically most intense on the head and upper chest, but is usually present on the lower chest and arms. This is a dark skinned child with measles. The child has conjunctivitis and coryza. The rash is papular, or raised, not flat. A measles rash is more difficult to see with dark skin. If the rash is accompanied by other symptoms, such as cough or conjunctivitis, measles is easier to diagnose.

If you see or hear about a person who had an influenza-like prodrome of cough, coryza, and fever, who then developed a rash, you should suspect measles. You should be **really** suspicious of measles if that person is unvaccinated or has recently traveled abroad. What should you do if you suspect measles? You should obtain a blood sample for serology and a specimen for viral isolation and notify your local or state health department as soon as possible. **Do not** wait until lab tests come back. Control measures must be started immediately, not a week or two later.

Measles – like varicella – is usually mild, but it can be a severe disease, associated with several complications. The most common complications of measles are diarrhea in 8%, and otitis media in about 7%. Pneumonia is reported in 6% of cases, and can be either viral or bacterial. Secondary bacterial pneumonias are often caused by *Streptococcus pneumoniae*, also known as pneumococcus. Pneumonia is also the most common cause of measles-related death. Encephalitis, which is inflammation of the brain, is reported in about 0.1% of reported cases, or 1 person per 1,000 cases. Hospitalization occurs in 18% of reported cases. Death from measles is now rare. In the late twentieth century, when measles was more common, death occurred in about 0.2% of reported cases, or about 2 deaths per 1,000 reported measles cases.

As with most diseases, complication rates are not equal across ages. You recall that most complications of pertussis occur among young children, and most deaths from tetanus occur among older adults. Measles is also age specific, but there are two peaks, not one.

This graph shows the percent of cases with pneumonia, the tan bar, and hospitalization, the green bar, by age. Preschool is on the left, school age is in the middle, and adults are on the right. Notice that there are two peaks, with almost equal rates of complications- children less than 5 years and adults 20 and older.

In summary, measles is an acute infectious disease, with a fairly typical clinical presentation. Complications are common, and occur most often in young children and adults.

The epidemiology of measles in the United States has changed dramatically, and more than once in just the last few years. These changes have had a major impact on immunization programs, so we will spend a little extra time discussing them.

Measles is a human disease. Even though it may have once been an animal disease, the reservoir is now only infected persons. There are no animal or insect reservoirs, and no chronic carrier state. Transmission is from person to person through the respiratory routes, either by way of droplets or by true airborne particles. Airborne transmission occurs through very small particles that remain suspended in the air. That means that direct contact with an infected person is not necessary to transmit the virus. Airborne transmission has mostly been described in closed settings such as medical exam rooms, or emergency department waiting rooms. Measles peaks in the late winter. It is communicable 4 days before to 4 days after rash onset. Maximum viral shedding occurs during the prodrome, before the rash appears.

Measles is a very contagious disease. Secondary attack rates of more than 90% have been documented. This means that a person with measles will infect almost every susceptible contact. The ease of transmission of measles can also lead to explosive outbreaks, particularly in unvaccinated populations.

This graph shows the number of measles cases reported by year since 1950. Before a vaccine was licensed in 1963, about 500,000 cases, and up to 1,000 deaths from measles were reported every year. In reality, there were 3 to 4 million cases per year. More than 90% of the population had been infected by 15 years of age. Measles incidence fell rapidly following vaccine licensure, and by 1970, reported measles cases had dropped more than 90% compared to just 10 years earlier.

This graph shows the number of reported cases of measles by year since 1980. From 1980 through 1988 an average of 3500 cases were reported per year. A major increase in measles began in late 1988. Cases increased further in 1989 and peaked in 1990 with more than 28,000 cases. This period is now referred to as the measles resurgence.

This resurgence provided dramatic and unfortunate evidence of the epidemic potential of measles. More than 55,000 cases and 125 measles deaths were reported during the 3 year period 1989 to 1991. The resurgence involved primarily unvaccinated preschool aged children, and led to large outbreaks in urban areas. It occurred because of low age appropriate vaccination levels. The realization that vaccine coverage was poor led directly to the Childhood Immunization Initiative of the 1990s, which gave us new immunization strategies, such as AFIX. These strategies are discussed in Chapter 3 of the text.

This graph shows the age distribution of reported measles cases from 1975 through 2002. The vertical axis shows the percent of reported cases in three age groups. School age children in pink, preschool children in blue, and adults in green. Notice that for many years, school aged children accounted for the majority of measles cases. In some years, up to 80% of cases were reported in this age group alone. During the 1980s, many outbreaks of measles occurred among high school and college students. Investigation of these outbreaks revealed that many of these children had already received one dose of measles vaccine. The outbreaks were occurring because of measles transmission among the small number of children in the school who had failed to respond to their first dose of vaccine. The desire to eliminate measles outbreaks in schools led to the 2-dose recommendation in 1989. We will discuss the 2-dose recommendation a little later when we talk about measles vaccine. Notice the contribution of preschool age children, shown in the blue line. There was a steady increase in cases in this group. In 1990, for the first time, more cases occurred in this age group than in school age children. This age shift was due to the measles resurgence of 1989 to 1991, and preschool age children remained the predominant group through the years of the resurgence. Since 1995 there has been no predominant age group for measles cases. All three groups account for about a third of the cases. But the biggest **proportionate** increase has been in the percent of cases contributed by adults. 20 years ago adults accounted for less than 10% of cases. Now they account for a third. Many of these cases in adults are international travelers and healthcare workers who are inadequately vaccinated.

Large outbreaks of measles among unvaccinated preschool age children characterized the measles resurgence of 1989 through 1991. Major immunization efforts were undertaken by immunization programs across the country. The result of these efforts was that measles immunization levels went up, and the outbreaks stopped. Measles vaccination levels among 2 year old children went from about 60% in the late 1980s to higher than 90% now. The result of these high levels of vaccination is record low numbers of measles cases.

Since 1997, less than 200 cases were reported per year. A record low annual total of only 44 cases was reported in 2002. The provisional total for 2003 is even lower – 42 cases. In fact, it appears that indigenous transmission of measles has been interrupted. Many of the cases are occurring in older children and adults who are either unvaccinated or have received only one dose of vaccine. Many cases occurring in the U.S. are a direct result of importation of measles virus from outside the country.

Importation of measles cases from outside the United States has been a particular problem in the last few years. During 1997 to 2001, imported cases accounted for 26% to 47% of all reported cases, with about half of the remaining cases linked to these importations. These cases occurred among both visitors and immigrants **to** the United States- including children adopted from outside the U.S. – and among American citizens **returning from** abroad. This underscores the need for U.S. residents to verify their immunity against measles before international travel.

For a few people with measles, the source of the virus is unknown. It is a high priority for us to determine the source of **all** measles cases reported in the United States. The measles laboratory at CDC has the technical capability to determine the geographic origin of viruses. But they need **your** help to obtain specimens. Specimens for viral isolation should be obtained on **every** suspected measles case that you see. We have included information about collection of specimens for virus isolation in your book. It is on page 132 of your text, at the end of the measles chapter.

Measles vaccine has gone through a number of changes in the more than 40 years since it was first developed. In 1963 two measles vaccines were licensed- a live attenuated vaccine and an inactivated vaccine. The virus used for both of these vaccines was called the Edmonston strain. It was named for David Edmonston, the child from whom the virus was isolated. The vaccine was very effective, BUT almost half the recipients developed fever or rash. In 1965 a live further attenuated vaccine was licensed, the Schwarz strain. This was and is an excellent vaccine. Although no longer used in the United States it is still used throughout the world. In 1967 the inactivated vaccine was withdrawn from the market. Considering the success of inactivated polio vaccine, an inactivated measles vaccine seemed like a good idea at the time. But *this* inactivated vaccine was ineffective. In fact, people who were vaccinated with this inactivated measles vaccine and then exposed to wild measles virus often developed an unusual illness called atypical measles. 1963 to 1967 are important dates to remember. If you identify someone who may have received inactivated measles vaccine during those years you should revaccinate them with live vaccine. In 1968 another live further attenuated vaccine, the Edmonston Enders strain was licensed. This is now the only measles vaccine available in the U.S. Finally, in 1971 a combined measles mumps and rubella vaccine was licensed- what we now know as MMR.

Measles vaccine is a live virus vaccine, and it behaves like you would expect a live virus vaccine to behave. The efficacy of a single dose has been estimated at 95%, with a range of 90 to 98%. Duration of immunity appears to be very long, probably lifelong. Even though single dose efficacy is 95%, the routine childhood schedule is 2 doses.

ACIP and the Academies of Pediatrics and Family Physicians recommend that MMR be used whenever one or more of its components are indicated. We do not recommend you routinely stock or use single antigen components of MMR. However, Merck does now have single antigen vaccines in stock if you need them. There may be some concerned but misguided parents who will only allow the use of single antigen measles, mumps, and rubella vaccines. We believe it is better to use single antigen vaccines than not to vaccinate the child at all. However, you should be aware that Merck will only sell single antigen measles, mumps, and rubella vaccines in packages of ten doses. And of course MMR and single antigen components may – and should – be administered simultaneously with all other childhood vaccines.

The age at which measles vaccination is recommended has changed several times since 1963. When first licensed in 1963, the vaccine was given at 9 months of age. In 1965 the age of vaccination was raised to 12 months and in 1976 to 15 months. Each of these changes followed data showing higher seroconversion rates at these older ages. In 1994, the recommended age returned to 12 months. This reduction in the recommended age of vaccination occurred because of a change in the **mothers** of children being vaccinated. People with measles **disease** generally develop higher levels of measles antibody than those who receive measles vaccine. Women who grew up in the prevaccination era usually contracted measles during childhood, so they passed lots of antibody to their infants during gestation. The situation was different in the 1990s. By then, most mothers had **not** had measles. If they were immune to measles at all it was probably because of vaccine. While **they** were immune, their infants received a smaller amount of passive antibody, that waned earlier in life. That is why the age of routine vaccination was lowered back to 12 months in 1994. Most infants in the U.S. are susceptible to measles by their first birthday. Are some children susceptible earlier? Yes. Do some children still have maternal antibodies at 12 months? Yes.

12 months is both the recommended age and the minimum age for MMR. This is because it is the earliest age at which almost all children have lost their maternal antibodies. What should you do if you find someone who was vaccinated **before** 12 months of age? Any dose of measles vaccine or MMR given before 12 months of age should **not** be counted as a valid dose. The child should be revaccinated on or after the first birthday. Doses given up to 4 days before the first birthday may be counted if your state accepts the grace period, as discussed in the General Recommendations.

Although measles vaccine is highly effective, not everyone responds to the first dose. Numerous studies conducted during the last 20 years have shown that 2% to 5% of recipients do not respond to the first dose, even given at the appropriate age. The reason why this small number of people do not respond to the vaccine is not known with certainty, but it is probably due to antibody present at the time of vaccination, or mishandled vaccine that was damaged, or recording errors, or possibly other causes. The good news is that vaccine failure is not permanent, and most people with vaccine failure of the first dose will respond to a second dose. More than 99% of persons with 2 doses of MMR after the first birthday will be immune. This is important, because to prevent measles outbreaks, nearly 100% of the population must be immune. Getting this high population immunity requires **two** doses of vaccine, not just one. The second dose of measles vaccine is intended to produce measles immunity in persons who failed to respond to the first dose, primarily to prevent outbreaks in schools. The second dose is **not** really a booster dose. It is possible that the second dose may increase antibody titers in some persons. But this increased antibody titer typically does not persist very long. The first dose of MMR is recommended at 12 to 15 months of age. The second dose should be routinely administered at 4 to 6 years of age, at entry to kindergarten or first grade. Entry to kindergarten or first grade is the **routine** age for the second dose. The second dose may be given at any time 4 weeks or more after the first dose. Any MMR dose given after the first birthday and at least 4 weeks after the first dose can be counted as a valid second dose. Second doses should be given to older children who have not had one. The adolescent visit at 11 or 12 years of age should be used as a check point, to make sure that **no** child enters young adulthood without two doses of MMR.

All adults born in 1957 or later should have received at least one dose of measles vaccine, or have some other evidence of measles immunity. But some adults are at increased risk of exposure to measles virus by virtue of their activities or occupation, and may need a **second** dose to assure that they are immune.

Adults at increased risk of exposure include college students, international travelers, and healthcare personnel. College students who live in dormitories are at particularly high risk. International travelers are at increased risk if they visit areas where measles is more common than it is in the U.S., which is almost everywhere in the world. College students and international travelers should receive two doses of measles vaccine if they do not have other evidence of measles immunity. Healthcare workers are at particularly high risk of measles, because they can unknowingly be exposed to measles at almost any time. Nosocomial measles transmission has been documented in the offices of private physicians, in emergency departments, and on hospital inpatient units. The risk of measles infection in medical personnel is estimated to be **thirteen times higher** than for the general population. So measles immunity in medical personnel is especially important. In 1997, ACIP and the Hospital Infection Control Practices Advisory Committee published comprehensive recommendations for the immunization of healthcare workers. These recommendations address **all** vaccines appropriate for healthcare workers, including MMR.

ACIP recommends that all persons who work in medical facilities should be immune to measles, not just those beginning employment, and not just those with direct patient care responsibilities. This recommendation includes students and volunteers, as well as medical and nonmedical employees.

People who were born in or after 1957 and now work in medical facilities should have serologic evidence of immunity, physician diagnosed measles, or documentation of TWO doses of measles vaccine. Because of the importance of measles immunity in health care workers, ACIP recommends that facilities consider a dose of measles vaccine for people born before 1957, unless they have other evidence of measles immunity.

You might have wondered what is so magic about 1957? It is generally assumed that persons born before 1957 are immune to measles because they had the disease as a child. But the 1957 cutoff for measles immunity is somewhat arbitrary. Seroprevalence studies in healthcare workers show that up to 5% of people born before 1957 **are** susceptible. 5% susceptible is probably okay for adults at low risk of exposure. But it is **not okay** if you're at high risk of exposure. And healthcare workers are among the most likely to be exposed to a person with measles. After all, where else would someone go who has a cough, a rash, and a 104 fever?

Let's talk now about adverse reactions following MMR vaccine. Since all three components of MMR are live viruses, adverse reactions following vaccination are predictable. They represent viral replication that leads to mild illness in susceptible vaccine recipients. This table shows the adverse reactions that occur following a dose of MMR vaccine. But not all the vaccine viruses cause all these reactions. Parotitis and deafness are rare adverse reactions usually attributed to the mumps component. We will discuss the adverse reactions associated with the rubella component a little later. This table highlights the adverse reactions that are attributed to the measles vaccine component. Please keep in mind, measles **disease** is more likely than vaccine to cause all these symptoms. The most common adverse reaction following measles vaccine is a low grade fever. This occurs in about 5% to 15% of recipients. Febrile seizures may follow. Antipyretics like acetaminophen or ibuprofen may prevent fever and febrile seizures. But because the onset of fever is often sudden and unpredictable, with live vaccines it is difficult to use antipyretics for this purpose. A rash occurs in about 5% of recipients, and lasts a day or two. This rash is much milder than the rash with measles disease. Thrombocytopenia, or low platelet count, is clinically apparent after less than one in 30,000 doses. It is usually transient and benign. On rare occasion, bleeding does occur. Encephalopathy is believed to occur after one in a million doses or less. This is a very rare event, again much less frequent than encephalopathy following measles disease.

Just as adverse reactions from measles vaccine mimic consequences of wild virus, they also mimic the **timing** of wild virus infection. That is, adverse reactions from measles vaccine generally occur 7 to 10 days after vaccination-after an incubation period of the virus. Many parents are concerned about an association between measles vaccine or MMR, and autism. This concern is amplified by sensational and unbalanced media. Many studies conducted in the last 2 or 3 years have provided evidence that there is NO association between MMR and autism. But parents will continue to ask questions, so you need to be familiar with the subject. Rather than go into detail here, we urge you to visit the National Immunization Program website, where there is an extensive amount of information on autism and vaccination, including a link to a 2001 Institute of Medicine Report on the topic.

Since measles vaccine is a live attenuated vaccine, it has a few more contraindications and precautions to vaccination than inactivated vaccines. A severe allergic reaction to a vaccine component or following a prior dose of vaccine is a contraindication, as it is for all vaccines. In the past, egg protein was believed to be responsible for the rare anaphylactic reaction following MMR vaccines. Evidence now suggests that gelatin, which is used as a stabilizer in MMR, may be the culprit. Measles and mumps vaccine viruses are grown in chick embryo fibroblast tissue culture and do not contain ovalbumin. Several studies have demonstrated the safety of MMR in egg allergic children. As a result, the ACIP and AAP recommend that you vaccinate – even egg allergic children – **without** prior skin testing or the use of protocols requiring gradually increasing doses of vaccine. Pregnancy is a contraindication to measles and MMR vaccines because of the theoretical risk of damage to a developing fetus. Neither measles vaccine nor MMR has ever been shown to injure a fetus. Although the manufacturer recommends otherwise, ACIP recommends that pregnancy should be delayed for 4 weeks after a dose of MMR. Measles vaccine virus is **not** transmittable. So pregnancy of a household contact is not a contraindication to vaccination of a child or other household member. Immunosuppression- which we use synonymously with immunodeficiency and immunocompromised- is also a contraindication to measles vaccine. MMR should not be given to persons taking large daily doses of oral or parenteral corticosteroids for more than 2 weeks. MMR should not be given to persons with cancer or those being treated for cancer. MMR should be delayed for at least one month after high dose steroids and at least 3 months after chemotherapy. I will reiterate that since measles vaccine virus is noncommunicable, there is no risk of transmission to a household contact. As a result, MMR is **recommended** for the healthy household contact of an immunosuppressed person.

A related issue is the use of MMR in people with HIV infection. Measles can be lethal to a person with HIV infection. So MMR continues to be recommended for people who have **asymptomatic HIV** infection. But MMR is not recommended for persons with evidence of **severe** immunosuppression from HIV. Severe immunosuppression is defined by low CD4 T lymphocyte counts or the percentage of total lymphocytes. There is more information about lymphocyte count criteria for severe immunosuppression on page 130 of the text, and in the MMR ACIP statement. Prevaccination HIV testing of an otherwise healthy person is not recommended.

There are two precautions for MMR. Moderate or severe acute illness is a precaution, and vaccination should be delayed until the acute illness improves. This precaution applies to all vaccines. Recent receipt of a blood product is a precaution because of potential inactivation of the vaccine virus. The vaccine and antibody table in Appendix A and in the General Recommendations should be your guide for timing of blood products and MMR.

One other issue I would like to mention is measles vaccine and tuberculin skin testing. It has been known for years that measles **disease** could cause a person with a latent tuberculosis infection to develop **active** TB. But measles **vaccine** does not exacerbate TB so TB testing is not a prerequisite for vaccination. In the

1960s, it was observed that the early measles vaccine – the Edmonston vaccine – could suppress the response to a tuberculin skin test, the PPD. Cell-mediated immunity is slightly suppressed by viral infections, including measles and measles vaccine. Cell-mediated immunity to TB antigens is what you are measuring with a PPD. If you give measles vaccine first, then place a PPD during the period of immune suppression, the response to the skin test may be reduced – even if the person **does** have TB. It is not known if the current, more attenuated vaccine also has this effect. But its safer to assume it does and not risk interference with the accurate reading of a PPD. To minimize the risk of interference between measles vaccine and PPD, you should apply the PPD at the same visit as MMR is administered. The mild immunosuppressive effect of the vaccine will not be a problem for a few days. This strategy avoids missing the opportunity for MMR vaccination. A second strategy is to apply the PPD first, and administer the MMR when the person comes back to have the PPD read. But if the person does not come back for the PPD reading, you have missed the chance to give the MMR. What you should **not** do is apply a PPD if MMR vaccine was already given. You should delay the PPD for 4 to 6 weeks if the MMR vaccine is administered first. By delaying the PPD – if MMR was already administered – you will eliminate the risk of vaccine suppression that could lead to a false negative skin test. A false negative PPD could delay treatment of a person with tuberculosis, which is not a good thing. We suggest you apply these PPD rules to **all** live injected vaccines, including smallpox vaccine, just to be safe.

So, in summary, measles has become a rare disease in the United States, due to high vaccination levels. Most remaining cases are imported from outside the U.S., and many of these cases are among adults. But without constant vigilance, measles could come back with a vengeance, like it did in 1990.